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Duvelisib: A Phosphoinositide-3 Kinase δ/γ Inhibitor for Chronic Lymphocytic Leukemia

Hima V. Vangapandu¹, Nitin Jain², and Varsha Gandhi^{1,*}

¹Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, 77054

²Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX 77030

Abstract

Introduction—Frontline chemotherapy is successful against chronic lymphocytic leukemia (CLL), but results in untoward toxicity. Further, prognostic factors, cytogenetic anomalies, and compensatory cellular signaling lead to therapy resistance or disease relapse. Therefore, for the past few years, development of targeted therapies is on the rise. PI3K is a major player in the B-cell receptor (BCR) signaling axis, which is critical for the survival and maintenance of B cells. Duvelisib, a PI3K δ/γ dual isoform specific inhibitor that induces apoptosis and reduces cytokine and chemokine levels *in vitro*, holds promise for CLL.

Areas covered—Herein, we review PI3K isoforms and their inhibitors in general, and duvelisib in particular; examine literature on preclinical investigations, pharmacokinetics and clinical studies of duvelisib either as single agent or in combination, for patients with CLL and other lymphoid malignancies.

Expert opinion—Duvelisib targets the PI3K δ isoform, which is necessary for cell proliferation and survival, and γ isoform, which is critical for cytokine signaling and pro-inflammatory responses from the microenvironment. In phase I clinical trials, duvelisib as a single agent showed promise for CLL and other lymphoid malignancies. Phase II and III trials of duvelisib alone or in combination with other agents are ongoing.

Keywords

CLL; Duvelisib; leukemia; PI3K; therapy

1. Introduction

Chronic lymphocytic leukemia (CLL) is a hematological malignancy of mature CD5+ and CD19+ B cells that primarily affects adults in the Western hemisphere, including approximately 25-30% of all leukemia in the United States, and has an overall incidence rate

*Corresponding Author: Varsha Gandhi (vgandhi@mdanderson.org), Phone: 713-792-2989, Fax: 713-745-1710.

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of 5% per year with increase prevalence in males [1-5]. CLL develops as a result of defective B-cell apoptotic machinery, which allows mature cells to accumulate without undergoing apoptosis and is associated with overexpression of anti-apoptotic proteins such as MCL1 and BCL2 family members [6], leading to a constitutively active B-cell signaling pathway (Figure 1). Prognostic factors including ZAP70 positivity and unmutated IGHV status favor B-cell signaling and mark refractory disease [7-9]. The standard of care for CLL has been chemoimmunotherapy comprised of combinations of fludarabine, cyclophosphamide and the anti-CD20 monoclonal antibody rituximab known as FCR therapy.

The emergence of effective targeted therapies has greatly transformed the range of treatment options for CLL patients. A better understanding of the biology of the disease has led to the approval of several targeted agents for CLL treatment, including ibrutinib, the BTK inhibitor, venetoclax, a BCL2 antagonist, and obinutuzumab, an anti-CD20 monoclonal antibody. In particular, the success of ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, induced new optimism for targeting the B-cell receptor pathway in CLL [10]. BTK is key downstream effector of the PI3K signaling pathway, the latter of which is crucial for B cell maintenance [11-14] and has been implicated in development of hematological malignancies [15, 16]. Several studies have demonstrated that activation of the PI3K δ isoform is upregulated in hematological malignancies [17, 18]. Further, inhibition of PI3K δ demonstrated impaired B cell signaling and proliferation [16]. Several pan-PI3K inhibitors have been developed and tested but were seen to have low therapeutic impact and high rates of toxicity, leading to the assessment of PI3K-isoform specific inhibitors including idelalisib, a PI3K δ inhibitor, which has been approved for B-cell malignancies, including CLL [19, 20]. We report here duvelisib, which targets the PI3K δ and γ isoform and has shown immunomodulatory and anti-proliferative activity, albeit with toxicity, in clinical trials for patients with hematological malignancies.

1.1. Phosphoinositide-3 kinase

Phosphoinositide-3 kinases (PI3Ks) are key signaling molecules that affect a diverse array of biological processes in cells, including proliferation, differentiation, survival, and metabolism [21-23]. PI3K, which is activated by receptor tyrosine kinases or G protein-coupled receptors, consists of two subunits: the p110 catalytic subunit and the p55/p85 regulatory subunit [21,24,25]. PI3K p110 phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP₂) on the 3'OH position to produce phosphatidylinositol 3,4,5-trisphosphate (PIP₃) [25-27]. PIP₃ functions as a second messenger and initiates a downstream signaling cascade by phosphorylating protein kinase B (AKT) via phosphoinositide-dependent kinase-1(PDK1) [28-29]. PI3K signaling is negatively regulated by PTEN, a phosphatase that converts PIP₃ back to PIP₂ [30]. AKT in turn modulates the activity of its downstream targets, mTOR, BAD, FOXO, p27, c-MYC, and cyclin D1 and regulates cellular proliferation, metabolism, and survival [31].

The PI3K family is categorized into three different classes (I-III) whose members are further differentiated based on their primary structure and substrate specificity [32]. Class I, comprised of the PI3K α , β , and δ isoforms, and class II, which includes the PI3K γ

isoform, are (thus far the most therapeutically relevant). These 4 isoforms are encoded by *PIK3CA*, *PIK3CB*, *PIK3CD*, and *PIK3CG*, respectively [33]. The α and β isoforms are responsible for cellular proliferation and insulin signaling, respectively [34]. Importantly, the PI3K p110 α and β isoforms are expressed ubiquitously, whereas the PI3K p110 δ and γ isoforms are expressed primarily in leukocytes.

2. Overview of the market

The PI3K Pathway in Solid Tumors and Hematologic Malignancies

PI3 kinases are mutated or overexpressed in several solid tumors, and are thus of high interest to investigators focused on those diseases. Early pan-PI3K inhibitors assessed in animal model systems included LY294002, wortmannin, and PX-866 [35, 36]. These inhibitors were only modestly efficacious, caused liver toxicity in mice [37], and did not possess the ideal pharmacological and pharmacokinetic profile in terms of dosing and specificity. The limitations of the pan-PI3K inhibitors led to the development of isoform-specific inhibitors (Table 1 and cited references). Because the PI3K δ and γ isoforms are exclusively expressed in hematopoietic cells [12, 38], several δ - or dual-isoform inhibitors (such as idelalisib, duvelisib, TGR-1202, AMG-319, and acalisib) have been tested in hematologic malignancies. Furthermore, owing to their impact on normal B and T cells, these PI3K inhibitors have been tested in several autoimmune diseases [39, 40].

Idelalisib, a PI3K δ inhibitor is FDA approved for use in combination with rituximab for the treatment of relapsed chronic lymphocytic leukemia (CLL) and follicular lymphoma. Several new agents are being developed or are already in preclinical proof-of-principle studies (Supplemental Table 1).

Duvelisib is first in human PI3K δ and γ inhibitor. Importantly, the PI3K δ and γ isoforms act synergistically, and their interplay elicits functional responses from immune cells [40, 41]. However, these isoforms differ in mode of their activation: PI3K δ is activated by tyrosine kinase or cytokine receptors, whereas, PI3K γ is activated by G protein-coupled receptor or RAS-mediated signaling. Inhibiting both isoforms may abrogate PI3K signaling and is more efficient than inhibiting either isoform alone in hematological malignancies and inflammatory diseases, providing the rationale for the design, synthesis and testing of PI3K δ/γ dual inhibitor, duvelisib.

3. Introduction to the compound

Duvelisib, also known as IPI-145 (Verastem; previously Infinity Pharmaceuticals), is an oral PI3K class I δ/γ inhibitor whose structure is similar to that of idelalisib. It was first developed as a PI3K δ inhibitor (known as INK 1197), that inhibits the PI3K γ isoform at higher concentrations. Duvelisib prevents the activation of PI3K γ and δ isoforms by binding competitively and reversibly to the p110 subunit's ATP binding pocket, which consists of a hinge region, a hydrophobic pocket not accessible to ATP, and a methionine residue that is above the adenine ring of ATP [42]. Duvelisib is 10 times more selective for PI3K δ than for PI3K γ ; the drug's IC₅₀ values for inhibiting the PI3K δ and γ isoforms are presented in Table 2.

3.1. Chemistry

Chemically, duvelisib is structurally similar to idelalisib (Box 1). When screened against various kinases ($n = >400$), duvelisib is highly selective against PI3K Class I isoforms, with little or no significant activity on Class II PI3K isoforms and other lipid kinases [43].

3.2. Preclinical Studies of Duvelisib

Duvelisib inhibits adaptive and innate immune responses [43], and therefore is used to treat autoimmune and inflammatory disease [44]. In mouse models of collagen-induced arthritis, duvelisib decreased joint damage by dampening matrix metalloproteinase-3 expression [44] and mitigated AKT phosphorylation compared to vehicle. The drug also diminished signs of arthritis in mice given autoantibodies against collagen type II. Duvelisib affected interleukin (IL)-17 production but not T-cell proliferation induced by collagen type II in splenocytes. Compared with vehicle-treated mice, those treated with 10 or 50 mg/kg duvelisib had lower autoantibody levels. Owing to its anti-inflammatory responses, duvelisib has promise for inflammatory diseases such as asthma, rheumatoid arthritis, and lupus nephritis [43, 45].

BCR axis has two critical enzymes; BTK and PI3K and inhibition of either results in abrogation of BCR pathway. In fact, duvelisib overcame the survival signals owing to a point mutation in the *BTK* gene (C481S) that rendered the CLL cells refractory to ibrutinib treatment in the clinic [46]. This observation has resulted in an interest in clinical trials of PI3K inhibitors for CLL patients who failed ibrutinib therapy.

Duvelisib has also been shown to overcome some of the survival benefits the microenvironment confers to CLL cells. Balakrishnan et al. demonstrated that duvelisib induces cell death in CLL lymphocytes, even in the presence of stromal microenvironment, and mitigates pseudoemperipolesis [47]. Ki67 and pAKT ser473 staining revealed that the drug also overcame cell proliferation signals after the cells were stimulated with a CD-40/IL-2/IL-10 cocktail, which mimics interaction with T cells [48]. Consistent with these data, duvelisib also abolished the protein expression of pERK1/2 T-202/Y-204 and pAKT Thr308 after stimulation with anti-IgM, at a minimal concentration of 0.01 μM , which suggested that the drug abrogates B-cell receptor-mediated signals. In addition, increasing doses of duvelisib, negatively correlated with CLL cell viability ($n = 12$) [46]. (The physiologically relevant concentration of duvelisib is 1 μM [47]). However, the drug was also partially cytotoxic to T cells and NK cells. Further study revealed that duvelisib treatment curbed CLL cells' cytokine signaling, including IL-2, TNF- α , and interferon γ signaling. Duvelisib treatment decreased BCR induced CCL3 and CCL4, chemokine secretion. Flow cytometric analysis of cell migration assays revealed that duvelisib curbed the migration of CLL cells towards SDF1 [47, 48]. Mechanism of duvelisib actions were associated with mitigation of AKT, BAD, ERK, and S6 activity, downstream of the B-cell receptor signaling cascade. Similar inhibitory events were reported in B-cell malignancies with idelalisib [49].

Duvelisib was also found to be effective in a murine xenograft model of CLL [50]. Treating CLL cells with 1 μM of the drug and injecting them into immunocompromised NSG (NOD-scid IL2R γ^{null}) mice resulted in the abrogation of B-cell and T-cell migration and

localization in tissues. Duvelisib's reduction of T-cell proliferation after activation further substantiates the benefit of impairing PI3K γ isoform signaling in *in vivo* models.

3.3. Pharmacokinetics and metabolism

Duvelisib's pharmacokinetics (PK) and pharmacodynamics (PD) were initially evaluated in patients with hematological malignancies and in healthy participants in a phase I clinical study [51]. The healthy participants received the drug as a single dose or multiple doses or twice a day (BID) for two weeks. Patients with hematological malignancies received the drug at 8 mg BID. PKs of the agent were measured after the initial dose as well at a steady-state concentration in both cohorts. The plasma concentration of the drug peaked 30-60 minutes after its administration, and the drug was eliminated after 3.5-9.5 hours when administered as a single dose, or 6.5-11.7 hours with multiple dosing. Accumulation of the drug was minimal after repeated dosing. Duvelisib at doses of up to 10 mg daily was well-tolerated in the healthy participants. The two groups had similar PI3K inhibition, which was assessed by measuring the surface expression of CD63 on basophils after *ex vivo* activation. Basophil CD63 surface expression declined in a dose-dependent manner; the maximum reduction, which corresponded with high plasma concentrations of duvelisib, occurred 1 hour after the drug administration. In patients with hematological malignancies, CD63 surface expression levels after 1 cycle (28 days) were at least 45% lower than those at the start of treatment.

4. Clinical Efficacy

Duvelisib has been tested in CLL patients in various settings. In a phase I study, the safety, maximum tolerated dose (MTD), and PD was assessed in 155 CLL patients, 44 of whom had relapsed/refractory (R/R) CLL [52]. The R/R CLL patients' median age was 67 years. In the R/R CLL cohort, 33 patients (75%) had at least 3 systemic therapies previously, and 14 of 32 patients tested (44%) had a 17p deletion. Duvelisib dose ranged from 8 mg to 75 mg; at a dose of 25 mg, the PI3K δ and γ isoforms were completely inhibited at a steady state. Duvelisib had clinical activity in the R/R cohort and rapidly caused lymphocytosis; absolute lymphocyte counts (ALC) returned to baseline within six 28-day cycles. After 2 cycles of duvelisib, 35 (79%) of the R/R CLL patients had reduced lymphadenopathy. Escalation of the duvelisib dose did not increase the severity of the drug's adverse effects. The overall response rate (ORR) was 52%; 1 patient had a complete remission, and 15 patients had partial remissions [52].

An early clinical trial of duvelisib enrolled 6 patients with R/R CLL as well as 6 patients with aggressive NHL who had acquired resistance to ibrutinib [53]. The Ki67 proliferation index of patients who had received ibrutinib was 18.4% higher than that of patients who had not received the drug. This proliferation was mitigated by two cycles of duvelisib treatment; however, the decrease was more prominent in the ibrutinib-naïve group. Another phase I trial tested single-agent duvelisib in 54 patients with R/R CLL, most of whom had undergone three or more systemic therapies previously, and almost half (n=26) harbored TP53 mutations or cytogenetic deletions (e.g., 17p-) that conveyed poor prognosis. [54]. In the 49 evaluable patients, duvelisib at 25 mg twice per day was efficacious in reducing

phospho-AKT levels, cell proliferation, and serum cytokine and chemokine levels. One patient (2%) had a complete response and 26 (53%) had partial responses, yielding an ORR of 55%. Adverse events (AE) were mainly grade 1 or 2 across the dose range.

The encouraging results from these early studies resulted in several late-phase trials to further assess duvelisib's efficacy in patients with CLL. For example, a phase III randomized blinded trial compared duvelisib to ofatumumab (DUO trial; NCT02004522) in patients with R/R CLL. Duvelisib in combination with obinutuzumab is currently being evaluated in CLL patients who previously received a BTK inhibitor (NCT02292225) and, in another ongoing study, duvelisib plus the established FCR (fludarabine, cyclophosphamide, rituximab) regimen is being tested in younger, treatment-naïve CLL patients (NCT02158091).

4.1. T-cell lymphomas

Duvelisib's inhibition of the PI3K γ isoform, which is also present in T cells, has also propounded the use of the agent in T-cell malignancies. A phase I clinical trial of duvelisib was undertaken in 33 patients with T-cell lymphoma, who received the drug twice a day for 28 days [55]. The patients' median age was 64 years, and their median number of previous therapies was 4. Of the 31 evaluable patients, the ORR was 42%. Levels of serum cytokines and chemokines were modulated within 8 days of treatment. However, more than 79% of the patients exhibited grade 3 adverse events that included increased alanine aminotransferase (ALT) (36%), rash (21%) and neutropenia (15%). Currently, duvelisib in combination with the histone deacetylase inhibitor romidepsin or proteasome inhibitor bortezomib is being tested in patients with T-cell lymphomas (NCT02783625).

4.2. Indolent NHLs

Duvelisib has been evaluated in patients with NHL, including in a phase I study of 32 patients with R/R indolent NHLs (iNHLs), [56]. The patients' median age was 65 years, and 19 patients (59%) had received at least 3 systemic therapies previously. At a duvelisib dose of 15-75 mg, cytokine and chemokine levels were mitigated through cycle 2 day 1. Dose responsiveness was not observed, as the degree of cytokine and chemokine reduction did not increase with dose. Patients had an ORR of 65%, and those with follicular iNHL, in whom duvelisib showed clinical activity by the first assessment, had a CR rate of 25%. The ORR and the drug's highly favorable safety profile indicated duvelisib monotherapy as a potential treatment for patients with R/R lymphomas. Based on the initial clinical activity and pharmacodynamics of the drug, a dosage of 25 mg BID was selected for phase II and III clinical trials of duvelisib. At this dose and schedule, a phase II investigation of duvelisib (DYNAMO, NCT01882803) was completed recently in 129 patients with iNHL [57]. Patients with follicular lymphoma (n=83), SLL (n=28), and MZL (n=18) had an overall response rate of 41, 68, and 33%, respectively. Progression-free survival was 8.4 months, and overall survival was 18.4 months. Additional studies of duvelisib alone and in combination with other agents for patients with follicular lymphoma are ongoing.

4.3. Safety and tolerability

As discussed above, duvelisib has exhibited clinical activity over a broad range of hematological malignancies. The drug is generally well tolerated in CLL, with the most

common adverse events predominantly being grade 1 and 2 across dose ranges of 25-75 mg. In the described Phase I study in R/R CLL, the most common AEs Grade 3 (10%, all causality) were transient cytopenias (neutropenia [31%] and thrombocytopenia [11%]), febrile neutropenia (15%), and pneumonia (11%). The most common reasons for treatment discontinuation were AEs (31%) and disease progression (24%) [54].

In both normal and neoplastic B-cells, recent investigations have demonstrated an increase in genomic instability after inhibition of PI3K through idelalisib or duvelisib [58]. This action was through the off target activity of the inhibitors on activation-induced cytidine deaminase.

Of interest, immune-mediated toxicities with the approved PI3K inhibitor idelalisib were recently reported. Severe diarrhea or colitis (grade 3 or higher) occurs in approximately 15% of patients treated with idelalisib monotherapy [59]. The risk is significantly higher (up to 40%) in patients who had not received any prior therapy for the CLL [60], and the onset of diarrhea/colitis is generally late (typically between 6-9 months after starting treatment). Serious and/or fatal hepatotoxicity occurs in approximately 15% of patients who receive idelalisib. Similar to colitis, the incidence of severe hepatotoxicity is significantly higher in previously-untreated patients. In a recent study, the risk of hepatotoxicity with idelalisib was very high (79% any grade, 54% grade 3 or higher) in previously-untreated patients with CLL [61]. Serious and/or fatal pneumonitis occurred in approximately 3-4% of patients who received idelalisib. The mechanism for the immune-mediated toxicity of this agent is likely related to suppression of Treg. A more robust immune system in previously untreated patients may have contributed to the higher rate of hepatotoxicity. In March 2016, an increased rate of death due to infectious complications was reported in several first-line phase III trials of idelalisib in patients with CLL and NHL, including an increased risk of *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV) infection was noted. Based on these data, FDA halted first-line trials with idelalisib. Toxicity data are not available for duvelisib in the front-line setting.

4.4. Regulatory affairs

At present, Duvelisib is not approved for use by the FDA.

5. Conclusions

In preclinical studies, duvelisib reduced cellular proliferation in response to BCR stimulus and mitigated cytokine signaling in CLL. Its activity as a single agent against ibrutinib-resistant R/R CLL and iNHL in early clinical trials has led to duvelisib's use in combination with other targeted agents in ongoing studies. Additional preclinical testing of these drug combinations will provide deeper insight into the future of duvelisib in the treatment of lymphoid malignancies.

6. Expert Opinion

Duvelisib's dual inhibition of the PI3K δ and γ isoforms has been exploited to treat leukemia and lymphomas as well as inflammatory and auto-immune diseases. Using

combinations of the drug with other agents as frontline therapy for CLL has yielded favorable responses.

Duvelisib has elicited responses in patients whose diseases are refractory to frontline therapies and who have failed ibrutinib treatment, underlining the importance of targeting PI3K δ/γ signaling in patients with poor prognosis. Duvelisib is also potent, overcoming survival and proliferation signals, even in the presence of lymph node and bone marrow microenvironments. The drug's suppression of chemokine signaling suggests that duvelisib's efficacy is in part due to its preventing CLL cells from homing to these microenvironments. Comprehensive *in vivo* studies, including those with validated mouse models, will help clarify the effects of this agent on the tumor microenvironment and identify novel drug combinations.

Idelalisib, a δ -specific inhibitor, and duvelisib, a δ/γ -selective agent, have both shown efficacy in preclinical and clinical investigations of CLL. However, the direct and indirect roles of PI3K γ signaling in CLL cells, T cells in the microenvironment, and other cells in the lymph nodes and the bone marrow are unknown; thus, additional studies are needed to delineate the impact of PI3K γ isoform inhibition on CLL cell survival signaling. The development of a γ -specific (δ -negative) PI3K antagonist could further elucidate this mechanism of action.

Duvelisib as a single agent evoked a few complete remissions and more frequent partial remissions in CLL patients, underscoring the need for combination strategies. Given the efficacy of a combination of idelalisib and rituximab (an anti-CD20 antibody) in CLL [59], clinical trials of duvelisib in combination with ofatumumab (another anti-CD20 antibody) in CLL patients previously treated with ibrutinib are in progress (NCT02004522).

One unique feature of agents that target the B-cell receptor axis is the development of lymphocytosis in treated patients. Caused by a migration of CLL cells from lymph node niches to the peripheral blood, this effect dissociates the microenvironment–CLL interaction that is otherwise prevalent in lymph nodes. However, this phenomenon also provides a challenge in targeting persistent malignant CLL cells in peripheral blood. The findings of one molecular analysis [62] suggest that these cells have increased BCL2 transcript and proteins. Our clinical *ex vivo* pharmacological profiling studies suggest that the combination of venetoclax, an exclusive BCL2 antagonist, and duvelisib has potential benefit in CLL [62]. This combination is being evaluated in R/R CLL patients who have not received other anti-PI3K or anti-BCL2 therapy (NCT02640833). Similarly, duvelisib is being evaluated with chemoimmunotherapy (FCR) in young CLL patients (NCT02158091) based on the rationale that CLL cells that have egressed in the blood after duvelisib therapy will be more accessible to the deleterious effect of chemoimmunotherapy. As noted previously, a phase I trial of duvelisib with the proteasome inhibitor bortezomib in patients with T-cell lymphomas is also underway. New PI3K inhibitors that also modulate other components of the BCR axis (e.g., mTOR) are being tested in early preclinical studies [63].

Overall, duvelisib holds great promise for CLL and other hematologic malignancies owing to its high specificity, manageable safety profile, and efficacy. Clinical results of randomized trials and combination therapies will further define its use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1**Drug Summary**

Drug Name	Duvelisib
Phase	I-III
Indication	Hematological Malignancies
Pharmacology description	PI3K δ/γ inhibitor
Route of administration	Oral
Chemical Structure

Pivotal Trial(s)	Flinn I, <i>et al</i> [52]; O'Brien, S <i>et al</i> [54]
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Figure 1. B cell receptor pathway and PI3K signaling

B cell receptor upon encountering an antigen, gets activated. CD79 (α , β) gets phosphorylated by SRC kinases, LYN and SYK, which in turn activates a signalosome. Along with CD19, BCR recruits PI3K to the membrane, where the latter phosphorylates PIP2 to PIP3. Catalytic subunits α , β and δ consist PI3K class IA isoforms and catalytic subunit γ belongs to class IB. p85 is the regulatory subunit that binds to class IA catalytic isoforms subunits, whereas p101/55 binds to catalytic subunit γ . These isoforms regulate various processes as indicated in the figure. Duvelisib inhibits δ and γ isoforms.

Table 1
Phosphoinositide-3 kinase (PI3K) inhibitors in clinical trials for cancer

Drug	Company	PI3K Specificity	Cancer	Clinical Trial Phase	Clinical Trial Status	Reference
Idelalisib	Gilead	δ	R/R CLL, lymphoma	I-III	FDA-approved	[17, 59,64,65]
Duvelisib	Verastem Previously Infinity	γ/δ	R/R CLL, lymphoma	I-III	Ongoing	[44, 46-48, 50, 53, 54-56]
TGR-1202	TG Therapeutics	δ	CLL, lymphoma	I-III	Ongoing	[66]
AMG319	Amgen	δ	B-cell malignancies, HNSCC	I	Ongoing	[67]
Acalisib	Gilead	β/δ	Lymphoid malignancies	I	Ongoing	[68]
Copanlisib	Bayer	Pan	MCL, iNHL, breast cancer, HNSCC	I-III	Ongoing	[69-71]
Pilaralisib	Exelixis	Pan	CLL, lymphoma, solid malignancies	I and II	Completed	[72, 73]
Buparlisib	Novartis	Pan	CLL, glioblastoma, breast cancer, lung cancer	I	Ongoing	[74-77]
SAR260301	Sanofi	β	Various	I	Ongoing	[78]
GSK2636771	GlaxoSmithKline	β	Lymphoma, prostate cancer, gastric cancer	I	Ongoing	[79]
PX-866	Oncothyreon	Pan	NSCLC, prostate cancer, glioblastoma	I and II	Ongoing	[80, 81]
Alpelisib	Novartis	α	Metastatic breast cancer	I-III	Ongoing	[82]
Pictilisib	Genentech	α/δ	Breast cancer, NSCLC	I	Ongoing	[83]
AZD8186	AstraZeneca	β/δ	NSCLC, prostate cancer, TNBC	I	Ongoing	[84, 85]
ZSTK474	Zenyaku Kogyo	Pan	Solid malignancies	I	Ongoing	[86-88]

R/R: relapsed/refractory; CLL: chronic lymphocytic leukemia; FDA: Food and Drug Administration; HNSCC: head and neck squamous cell carcinoma; MCL: mantle cell lymphoma; iNHL: indolent non-Hodgkin lymphoma; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

Table 2
Pharmacodynamics of duvelisib

PI3K Isoform	IC ₅₀ , nM	K _D , pM
δ	96	23
γ	1028	243